

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
24 June 2004 (24.06.2004)

PCT

(10) International Publication Number  
**WO 2004/052851 A1**

(51) International Patent Classification<sup>7</sup>: **C07D 207/26**,  
409/12, 401/12, 413/14, 405/12, 417/14, 417/06, 409/14,  
A61K 31/4025

(21) International Application Number:  
**PCT/EP2003/013799**

(22) International Filing Date: 4 December 2003 (04.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0228552.6 6 December 2002 (06.12.2002) GB

(71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED [GB/GB]**; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

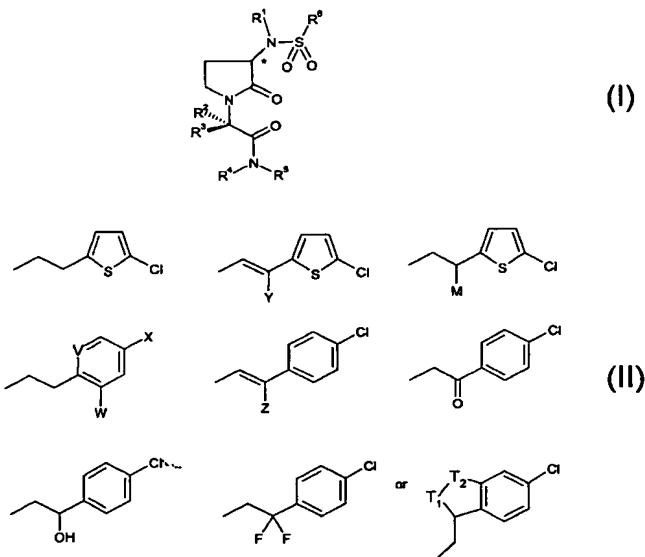
(72) Inventors; and

(75) Inventors/Applicants (for US only): **BORTHWICK, Alan, David [GB/GB]**; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **CHAN,**

**Chuen [GB/GB]**; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **KELLY, Henry, Anderson [GB/GB]**; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **PEACE, Simon [GB/GB]**; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **SENGER, Stefan [GB/GB]**; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **SHAH, Gita, Punjabhai [GB/GB]**; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **SMITH, Stephen, Allan [GB/GB]**; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **SMITH, Steven [GB/GB]**; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SN1 2NY (GB). **WATSON, Nigel, Stephen [GB/GB]**; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **WEST, Robert, Ian [GB/GB]**; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **YOUNG, Robert, John [GB/GB]**; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

[Continued on next page]

(54) Title: PYRROLYDIN-2-ONE DERIVATIVES AS INHIBITORS OF THROMBIN AND FACTOR XA



(57) Abstract: The invention relates to compounds of formula (I), wherein : R<sup>1</sup> represents hydrogen, C<sub>1-4</sub> alkyl, -CH<sub>2</sub>CO<sub>2</sub>H, -CH<sub>2</sub>CO<sub>2</sub>C<sub>1-2</sub>alkyl, or -CH<sub>2</sub>CONR<sup>7</sup>R<sup>8</sup>; R<sup>2</sup> and R<sup>3</sup> independently represent hydrogen, -C<sub>1-6</sub>alkyl, -C<sub>1-3</sub>alkylCN, -C<sub>1-3</sub>alkylCO<sub>2</sub>H, -C<sub>1-4</sub>alkylOC<sub>1-4</sub>alkyl, -C<sub>1-4</sub>alkylS(O)<sub>n</sub>C<sub>1-4</sub>alkyl, -C<sub>1-4</sub>alkylN<sup>10</sup>R<sup>11</sup>, -C<sub>1-3</sub>alkylNCO<sub>2</sub>C<sub>1-4</sub>alkyl, -C<sub>1-3</sub>alkylCONR<sup>7</sup>R<sup>8</sup>, -C<sub>1-3</sub>alkylCO<sub>2</sub>C<sub>0-2</sub>alkylR<sup>9</sup>, -C<sub>1-3</sub>alkylCOOC<sub>0-2</sub>alkylR<sup>9</sup>, -C<sub>1-3</sub>alkylCON(R<sup>8</sup>)C<sub>0-2</sub>alkylR<sup>9</sup>, -C<sub>1-3</sub>alkylNCO<sub>2</sub>C<sub>0-2</sub>alkylR<sup>9</sup>, -C<sub>1-3</sub>alkylNCOOC<sub>0-2</sub>alkylR<sup>9</sup> or -C<sub>0-2</sub>alkylR<sup>9</sup>, with the proviso that one of R<sup>2</sup> and R<sup>3</sup> is hydrogen and the other is a substituent other than hydrogen; n is an integer between 0 and 2; R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached form a morpholino ring; R<sup>6</sup> represents a group selected from formula (II) wherein T<sub>1</sub> and T<sub>2</sub> independently represent CH<sub>2</sub>, NH, S or O with the proviso that when one of T<sub>1</sub> or T<sub>2</sub> represents NH, S or O the other represents CH<sub>2</sub>; M represents CH<sub>3</sub>, -OH or PO; V represents CH or N; W represents H, CH<sub>3</sub>, Cl or F; X represents Cl, Br, F or -CH<sub>3</sub>; Y represents CH<sub>3</sub> or CF<sub>3</sub>; Z represents -CH<sub>3</sub> or F; R<sup>7</sup> and R<sup>8</sup> are

independently hydrogen, C<sub>1-4</sub>alkyl or together with the N atom to which they are bonded form a 5- or 6-membered non-aromatic heterocyclic ring, optionally containing an additional heteroatom selected from O, N or S; R<sup>10</sup> and R<sup>11</sup> independently represent C<sub>1-4</sub>alkyl or together with the N atom to which they are bonded form a 5- or 6-membered non-aromatic heterocyclic ring, optionally containing an additional heteroatom selected from O, N or S; R<sup>9</sup> represents phenyl or a 5- or 6-membered aromatic or non-aromatic heterocyclic group, containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by 0-2 groups selected from: C<sub>1-3</sub>alkyl or halogen; and pharmaceutically acceptable derivatives thereof, processes for their preparation, pharmaceutical compositions containing them and to their use in medicine, particularly use in the amelioration of a clinical condition for which a thrombin inhibitor is indicated.

WO 2004/052851 A1



(74) **Agent:** BAKER, Suzanne, Jane; GlaxoSmithKline, Corporate Intellectual Property CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(81) **Designated States (national):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) **Designated States (regional):** ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

— with international search report

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*